

Procter & Gamble

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2791 '99 NOV 2

November 1, 1999

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm. 1061
Rockville, MD 20852

Re: Docket Number 99F-2729

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the Draft Guidance for Industry, BA and BE Studies for Orally Administered Drug Products – General Considerations. We have the following comments.

General comment:

The guidance proposes using replicate designs to assess the frequency of S*F interactions in a variety of situations. We are unaware of a significant body of data that suggest that this approach is necessary. We propose that these effects be studied through PQRI before implementation of replicate design requirements. Based on our current understanding of factors that may lead to S*F interactions, model drugs should be identified that are likely to exhibit a S*F interactions and studies be adequately designed to appropriately assess the potential for interactions. This approach would provide meaningful data to assess the need for replicate designs instead of just broadly implementing them.

Specific comments:

1. III.A.4. -- This section suggests that replicate designs be used for a wide range of studies with some specific exceptions. FDA has failed to establish that replicate designs should be used for any dosage form. Instead of requiring wide-spread implementation for replicate designs, it should establish specific instances where replicate designs would be useful and allow their use in these instances.

In the same section, replicate designs should not be required for the comparison of the Phase 3 and marketed formulations because this change is a question of prescribability, not switchability in the IND period, as there is no switchability issue to be addressed.

2. III.A.8.a. -- Change the last sentence to read: "A minimum of two quantifiable samples after dosing should be collected" Addition of the underlined words clarifies the sampling requirements.

3. III.A.8.c. last bullet, second line – for clarity, add "observed" between last and measurable.

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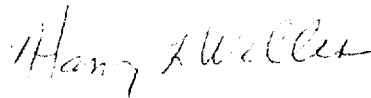
An added concern related to the guidance is the possibility of implementation of individual bioequivalence requirements for a two year interim period as was discussed in the recent Office of Pharmaceutical Sciences Advisory Committee meeting. If IBE is implemented as described for an interim period, what will happen after the 2 year period if:

- 1) The new formulation passes IBE but fails ABE and following the 2 year period, IBE is no longer used or the criteria/approach is modified. Is the new formulation recalled?
- 2) The new formulation passes ABE but fails IBE (it is approved since it specified a priori in the protocol that it would use ABE criteria) and IBE is required following the 2 year period. Since data are available indicating that the new formulation failed IBE, will this product be recalled?

Will not the proposed interim period create more problems in the future with more "grandfathered" products, which FDA has been trying to minimize?

If there are any questions or if I can be of further assistance, feel free to call on me. My phone number is 513-622-3914 and my email address is welles.hl@pg.com.

Sincerely,



Harry L. Welles, Ph.D.
Principal Scientist
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